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10/772,704	02/05/2004	George C. Tsokos	Army 178	5604

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/772,704
Filing Date: February 05, 2004
Appellant(s): TSOKOS ET AL.

Caroline Nash
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 06/22/2009 appealing from the Office action mailed 12/12/2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6159697	MONIA	12-2000
7345025	SYMONDS	3-2008
20030134415	GRUENBERG	7-2003

Weintraub, HM. "Antisense RNA and DNA." Scientific American, 1990, pp 40-46.

Solomou et al. "Molecular Basis of Deficient IL-1 Production in T Cells from Patients with Systemic Lupus Erythematosus." The Journal of Immunology, 2001, Vol. 166: pp 4216-4222.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

Claims 1, 10-11, 15, 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Solomou et al. (cited in PTO form 1449 filed 09/24/2004), Weintraub (Scientific American, 1990), Monia et al. (US Patent No. 6,159,697), Symonds et al. (US Patent No. 7,345,025) and Gruenberg et al. (US 20030134415).

The instant claims are drawn to a method of increasing IL-2 production in systemic lupus erythematosus (SLE) T cells in a patient that has SLE comprising

administering gene modified T cells to said patient, said T cells having been modified with an antisense cAMP response element modulator (CREM) or a plasmid vector expressing an antisense CREM, thereby increasing the expression of IL-2 in said T cells in said patient. The instant claims are also drawn to a method of increasing IL-2 production in T cells from a SLE patient comprising removing T cells from a patient and treating said T cells with an antisense CREM to increase IL-2 production. It must be noted that "leukophoresed lymphocytes" are not defined in the specification and because T cells belong to a group of white blood cells called lymphocytes, leukophoresed lymphocytes for purpose of prior art considered T cells.

Solomou et al. teach a method of increasing IL-2 production in T cells harvested from patients with SLE (see abstract). Solomou et al. teach IL-2 is a growth factor for T lymphocytes and is exclusively provided by T cells and further teach T cells from SLE patients produced decreased amount of IL-2 (see page 4216). Solomou et al. teach the decreased production of IL-2 in SLE T cells is a result of gene transcriptional repression mediated by the binding of CREM (see page 4216). Solomou et al. teach SLE T cells have increased levels of CREM and show CREM is a strong repressor of IL-2 production. Solomou et al. teach SLE patients with decreased T cells functions are more susceptible to life-threatening infections (see page 4216). Solomou et al. does not teach modifying T cells with an antisense targeted to CREM and does not teach a method of administering the modified T cells to a SLE patient.

Weintraub teach that antisense oligonucleotides can be synthesized to hybridize to any target sequence and inhibit expression of any protein provided the target gene is

known (see page 42). Monia et al. teach general antisense targeting guidelines and teach targeting any region of a desired target (see columns 3-6 generally) and teach antisense compounds can be delivered to cells in a plasmid (see column 2). Monia et al. teach antisense compounds are commonly used as research reagents and diagnostics and teach such antisense compounds can be used in methods to inhibit the expression from a target gene and in methods of treatment of diseases.

Symonds et al. teach genetically modifying any type of progenitor cell with antisense molecules and reinfusing these cells into patients for therapeutic treatments (see columns 13-16).

Gruenberg teach a method of producing a population of immune cells for use in adoptive immunotherapy. Gruenberg teach T lymphocytes can be harvested from patients, enriched and then infused back into a patient and teach the cells have therapeutic applications in patients suffering from a variety of diseases such as SLE (see page 2, especially paragraph 0014 and 0015).

A person of ordinary skill in the art, upon reading Solomou et al., would have recognized the desirability of increasing IL-2 production by inhibition of the suppressor protein CREM in SLE patients. Both Weintraub and Monia et al. teach a known method of inhibiting expression of a target gene using antisense molecules. Furthermore, Gruenberg et al. teach method of treating patients with SLE using T cells that would reasonably been expected to be applicable to a method of increasing IL-2 in SLE patients. Further, Symonds et al. teach methods of genetically modifying progenitor cells from a patient using antisense molecules that would reasonably been expected to

be applicable to genetically modifying T cells with an antisense compound, as instantly claimed. Therefore, because Weintraub teach any antisense can be synthesized to target any gene if the cDNA is known and Monia et al. is considered to comprise detailed instructions on how to make and use antisense compounds to any target, it would have been obvious one of ordinary skill in the art to try the methods taught by Weintraub and Monia et al. to decrease the expression of CREM protein in an effort to increase the production of IL-2 in SLE patients.

Thus, because it is taught in the prior art how to inhibit expression from any target gene and it was known in the prior art that inhibition of the expression of the IL-2 suppressor increases IL-2 production in T cells of SLE patients, which have been taught to have therapeutic effects SLE patients, it would have been obvious to genetically modify T cells to inhibit CREM expression in an effort increase IL-2 production in SLE patients.

(10) Response to Argument

Appellant argues that none of the cited references alone or in combination would have provided the necessary teaching to enable and motivate one of ordinary skill in the art to arrive at the presently claimed invention because none of them conclude that CREM alone is responsible for decreased IL-2 production in SLE patients. Appellant argues that the results reported by Solomou et al. showing decreased IL-2 production in T cells of Lupus patients and increased amounts of CREM bound to the IL-2 promoter, inhibiting the production of normal levels of IL-2, was very early work in the field.

Appellant argues it was not known "why CREM bound to the IL-2 promoter in Lupus patient's T-cells" and it was not known "how to stop CREM from binding to the IL-2 promoter" and at the time much was unknown about the pathways of CREM binding in Lupus patients. Appellant argues that from Solomou et al. one of ordinary skill in the art would have understood that multiple transcriptional factors could be the problem and there is no support provided that using antisense CREM would help SLE patients.

Appellant further argues Weintraub is directed at the basic teachings that molecules that bind with specific mRNA can selectively turn off genes and does not teach that disease wherein defective genes are present in lymphocytes could be treated. Appellant argues Monia et al. teach antisense inhibition in endothelial cells which are totally different than T-cells and there is no suggestion that antisense technology would be effective for all types of cells, particularly the instantly claimed T cells.

Appellant argues that "Symonds et al. has been cited by the Examiner for the proposition that antisense would have been the cure for any disease that had a symptom of a high level of a protein" and further argues is not directed to the claimed highly complex immunological T cells and did not solve the mystery of why CREM is increased in SLE T cells and whether there were other transcriptional factors that effect IL-2 production or why CREM production decreased in SLE patients following stimulation.

Gruenberg et al. is the only reference that relates to T-cells according to Appellant but unlike the present invention, Gruenberg et al. operated without any growth

factors like IL-2 or IFN-gamma and required re-stimulation to obtain a pure population of activated Th1 memory cells. Appellant further argues that Gruenberg et al. do not teach that antisense would be effective in T-cells and lack teachings that suggest CREM is the only reason that IL-2 production is decreased in SLE patients.

Appellant's arguments are not convincing. Appellant agrees that Solomou et al teach that it was desirable to increase IL-2 production in SLE patients and that CREM was directly responsible for decreased IL-2 production. Appellants argument that it was not known "why CREM bound to the IL-2 promoter in Lupus patient's T-cells" and it was not known "how to stop CREM from binding to the IL-2 promoter", is irrelevant because the instant invention is not drawn to methods of determining why CREM binds to the IL-2 promoter in Lupus patients. Solomou et al. teach IL-2 is a growth factor for T lymphocytes and is exclusively provided by T cells and further teach T cells from SLE patients produced decreased amount of IL-2 and states that SLE patients with decreased T cells functions are more susceptible to life-threatening infections. A person of ordinary skill in the art would have wanted to increase the T cells in SLE patients in methods of treatment and given it was known in the art that IL-2 is needed as a growth factor to T cells, would have taken from Solomou et al. that CREM was directly responsible for a decreased level of IL-2 expression in T cells of SLE patients. While Solomou et al. do not teach how to stop CREM from binding to the IL-2 promoter, one of ordinary skill in the art would have looked to the most efficient way to inhibit CREM expression such that CREM was not capable of binding to the IL-2 promoter and preventing expression of IL-2 in T cells.

It was known in the art at the time of filing of the instant invention that antisense technology was an efficient way to decrease expression from an undesirable gene to prevent the expressed protein from causing unwanted deleterious effects in certain processes and pathways in cells. Because both Weintraub and Monia et al. teach known methods of inhibiting expression of a target gene using antisense molecules, it would have been a matter of routine experimentation to design an antisense compound targeted to a gene encoding CREM. Weintraub was not cited to teach that diseases wherein defective genes are present in lymphocytes could be treated but was cited for the basic teachings that molecules that bind with specific mRNA can selectively turn off genes as stated by Appellant and is an early reference cited for the teachings that if a gene cDNA is known, one of ordinary skill in the art would be capable of making an antisense compound targeted to that gene. Monia et al. is considered to comprise detailed instructions on making and using antisense compounds to inhibit gene expression in a desired cell for the purpose of providing treatment effects and teach that antisense compounds has been successfully used in cells, tissues and animals and is currently being used in clinical trials.

While Monia et al. do not specifically exemplify transfection of a T cell with an antisense molecule; Symonds et al. teach genetically modifying hematopoietic cells ex vivo with antisense molecules and reinfusing these cells into patients for therapeutic treatments that would reasonably be expected to be applicable to genetically modifying T cells, which are differentiated hematopoietic cells, with an antisense compound as claimed. Further, given that Gruenberg teach T lymphocytes can be harvested from

patients, enriched and then infused back into a patient and teach these cells have therapeutic applications in patients suffering from a variety of diseases such as SLE, it would have been obvious to genetically modify lymphocytes with an antisense compound targeted to CREM and re-infuse these cells into an SLE patient in methods to increase IL-2 production in said patients.

Symonds et al. was not cited for the proposition that antisense would have been the cure for any disease that had a symptom of a high level of a protein as stated by Appellant. Symonds et al. teach detailed methods for obtaining hematopoietic cells from the blood of patients, transfecting antisense molecules using plasmid vectors into said cells and re-infusing these cells back into a patient and one of ordinary skill in the art would looked to Symonds et al. and been reasonably capable of using said methods to transfect an antisense molecule targeted to CREM in T cells in an effort to reduce the expression of CREM such that IL-2 production would be increased in SLE patients.

In response to Gruenberg et al. not teaching the use of growth factors, the instant claims do not require the use of any growth factors. The methods taught by Gruenberg et al. would have reasonably been expected to be applicable to a method of increasing IL-2 in SLE patients. The fact that Gruenberg et al. lack teachings that suggest CREM is the only reason that IL-2 production is decreased in SLE patients is irrelevant to the instantly claimed invention because the claimed invention is not drawn to methods of determining what other factors are responsible for a decreased IL-2 production in SLE patients.

Solomou et al. clearly teach that it was desirable to increase IL-2 production in SLE patients and that CREM was directly responsible for decreased IL-2 production and this finding by Solomou et al. provides one of ordinary skill in the art the desire to target CREM in efforts to increase IL-2 production in SLE patients and given it was known in the art that antisense technologies efficiently reduce expression of an undesired target gene and can be made to target any gene and given that therapeutic applications using re-infused T cells in patients suffering from SLE were known as well as methods of genetically modifying hematopoietic cells with antisense compounds, which are precursors to T cells, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Kimberly Chong/

Primary Examiner AU1635

Conferees:

/JD Schultz/

Supervisory Patent Examiner, Art Unit 1635

/Ram R. Shukla/

Supervisory Patent Examiner, Art Unit 1644